Remarks

The specification has been amended at page 7 with the paragraph starting at line 65 to incorporate the text of the original claims 6-9 as filed. No new matter has been added with the amendments to the specification.

Claims 4-10, 12-20 and 24-27 are pending.

Claims 6, 9, 24 and 26 have been amended. Support for the amendments is in original Claims 1-3 and Claim 24, and the specification at page 6, line 37 ("between" 10:1 and 1:1).

No new matter has been added with the amendments to the claims, which are intended to merely clarify language in the claims and the subject matter claimed. The scope of the claims is intended to be the same after an amendment as it was before the amendment.

The Examiner indicated that Claim 9 was "free of prior art." Claim 9 has been amended to be independent and to incorporate the limitations of the base claim – Claim 24. Allowance of Claim 9 is respectfully requested.

Objection to Specification

The Examiner objected to the specification under 37 CFR §1.75(d)(1) and MPEP §608.02(0) for lack of antecedent basis for the claimed subject matter in original Claims 7-9.

The specification has been amended at page 7 to incorporate the subject matter recited in original Claims 7-9.

The original claims as filed are part of the specification. (35 USC § 112, 2d par.) *Northern Telecom, Inc. v. Datapoint Corp* , 15 USPQ2d 1321, 1326 (Fed.Cir. 1990); *In re Benno*, 226 USPQ 683, 686-87 (Fed. Cir. 1985). The amendment simply conforms the text of the specification to the claims and thus do not broaden the disclosure.

Rejection of Claims under 25 USC §112(1)

The Examiner rejected Claims 4-10, 12-20 and 24-27 under Section §112(1) as non-enabled.

Claims 24 and 26 have been amended to recite the molar ratio as "between 10:1 and 1:1."

Regarding Claim 6, the specification at page 7 to incorporate the subject matter recited in original Claim 6. It is noted that original claim 6 depended from original claim 3, which was subsequently canceled. Claim 6 has now been amended in independent form.

Accordingly, it is submitted that the claims as presented are fully enabled, and withdrawal of this rejection of the claims is respectfully requested.

Rejection of Claims under 35 U.S.C. §112(2)

The Examiner rejected Claim 6 under Section 112(2) as indefinite for reciting the limitation "molar ratio is 10:3."

Claim 6 has been amended as an independent claim to include the limitations of the base Claim 24 (limitations previously recited in original Claim 1-3 from which *original* Claim 6 depended).

Accordingly, it is submitted that Claim 6 as amended is clear in its meaning, and withdrawal of this rejection is respectfully requested.

Rejection of Claims under 35 USC §193(a)

The Examiner rejected Claims 4-8, 12-16, 19-20 and 24-27 under Section 103(a) as obvious over USP 5,773,027 (Bergeron) in view of Cantin et al. (*J. Virology* 71(2): 1922-1930, March 1997).

The Examiner rejected Claims 10 and 17-18 as obvious over Bergeron in view of Cantin, further in view of Desormeaux (*J. Drug Targeting* 6(1): 1-15, 1998).

The Examiner rejected Claim 20 as obvious over Bergeron in view of Cantin, further in view of Harlow (*Antibodies, a Laboratory Manual*, 1988, Cold Spring Harbor, NY, pp. 620-629) and Desormeaux.

These rejections are respectfully traversed.

The cited references fail to teach or suggest Applicant's formulation that comprises an anti-HLA-DR antibody coupled to a liposome, which is capable of binding to an HLA-DR protein present on both the surface of an infectious agent *and* at the membrane surface of a cell.

The Examiner cites to Bergeron for teaching a formulation for treating a viral disease such as HIV that comprises a liposome composed of a mixture of diacylphosphatidylcholine and

diacylphosphatidylglycerol, including coupling of antibody molecules to the liposome to enhance targeting of the liposome to specific cells, citing to col. 4, lines 11-13.

The Examine maintains that it would be obvious to substitute an anti-HLA-DR antibody as disclosed by Cantin in the formulation taught by Bergeron. The Examiner further asserts that one skilled in the art would have a reasonable expectation of success in producing the claimed invention based on the combined teachings of the references – Bergeron and Cantin.

Bergeron describes antiviral agents encapsulated in liposome. The only reference to the use of antibodies is a *general statement* at col. 4, lines 9-14, that liposome-encapsulated drugs include immunoliposomes that are "modified by the coupling of antibody molecules which enhance the targeting of specific *cells*."

Bergeron provides *no* examples of any antibodies and *no* teaching of how such coupling is achieved. Other than a general statement, Bergeron provides no guidance or other information that would lead to Applicant's invention.

Furthermore, the statement in Bergeron relates only to antibody molecules that enhance *targeting of specific cells*. Bergeron says nothing about antibodies to target an infectious agent.

The Examiner cites Cantin for teaching an anti-HLA-DR antibody 2.06 that binds to the surface of HIV-1 virions *and* a host cell membrane (see Office Action at page 5, emphasis added):

> Catin et al teach antibody such as anti-HLA-DR 2.06 (class II MHC) that binds to HLA protein present at the surface of an infectious agent such as HIV-1 virions *and at the surface of a host cell membrane* such as CD4+ T cells and macrophage (see entire document, page 1923, col. 2, Antibodies, page 1925, col. 1…in particular).

The Examiner's interpretation of Cantin is incorrect.

First of all, Cantin describes reacting 2.06 only with HIV-1 particles.

Cantin does *not* disclose reacting *2.06* with *cells* – *or* reacting *a liposome-bound 2.06* with *viral particles and much less cells.*

Rather, Cantin discloses reacting antibody *L243*[1] with cells – transfected 293 T cells (single MHC-II isotype, HLA-DR1). See page 1923, col. 2 (Flow cytometric analysis of cell surface and internal antigens).

Secondly, Cantin describes reacting 2.06 with *specially produced virus stock*[2] expressing a *single* MHC-II isotype – namely the *HLA-DR1 allele* (see pp. 1928-1929, bridging sentence).

Cantin does not disclose reacting antibody with HIV-1 virions from primary isolates, macrophages, or blood plasma, for example, which would include the highly polymorphic HLA-DR locus, nor cells that express all MHC-II isotypes (DR, DP, DQ) on their surfaces. Cantin particularly states that the described work does not relate to infectivities of virions on primary monocyte-derived macrophages (page 1928, 2nd col.):

> In this work, we have not tried to compare the infectivities of virions bearing or not bearing HLA-DR1 on primary monocyte-derived macrophages…These studies are needed, since monocytes/macrophayes are also infected in vivo with HIV and are thought to play a key role in the pathogenesis of the disease…Moreover, virally infected monocytes/macrophages are potent producers of HLA-DR bearing virions because they are known to express on their surfaces all MHC-II isotypes (DR, DP, and DQ)…

As acknowledged by Cantin, the HLA-DR locus is *highly polymorphic*, and the affinity between HLA-DR and CD4 on a cell surface may vary according to the HLA-DR allele (p. 1929, col. 1). See also, Cantin at pp. 1928-1929, bridging sentence ("…this work focused on a single HLA-DR allele, namely HLA-DR1…").

At page 7, 1st paragraph, the Examiner stated (emphasis added):

> …In fact, the same monoclonal antibody anti-HLA-DR (clone 2.06, IgG1) as taught by Cantin et al. was used by applicants, see instant specification at pages 12, lines 7-8. *One skilled in the art reading the specification* would expect a monoclonal anti-HLA-DR 2.06 antibody from the same clone would necessarily and inevitably bind to the same HLA-DR protein on both host cell expressing HLA-DR and on HIV virions that have incorporated the host HLA-DR protein.

It is clear from the foregoing statement that the Examiner is *impermissibly* utilizing Applicant's disclosure as a guide for combining the references.

It is also clear that it is only through hindsight reconstruction utilizing Applicant's disclosure, that the Examiner can say that the cited references teach a formulation of liposomes

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[1] L243 is described as an antibody specific for non-polymorphic determinant of HLA-DR α β dimer.

[2] The virus stock HXB-Luc HLA-DR1/POS was produced by a transiently transfected 293 T cell line (no detectable surface expression of any MHC-II isotype) with expression vectors encoding α and β chains of HLA-DR1.

coupled to an antibody to target *both* cells and virus. The Examiner has given no good basis why a skilled artisan with no knowledge of the invention, would select the elements from the cited references for combination in the manner claimed.

One skilled in the art reading Bergeron would not be motivated to utilize antibody 2.06 of Cantin for coupling to the described liposome-enclosed drugs. Bergeron generally teaches coupling an antibody to liposomes to enhance targeting of specific *cells*. By comparison, Cantin discloses use of antibody 2.06 to target special *HIV-1 particles —not cells.*

Furthermore, based on Cantin's disclosure, one skilled in the art would not expect monoclonal anti-HLA-DR1 2.06 antibody would necessarily and inevitably bind to HLA-DR *protein* on *both host cells* expressing HLA-DR *protein* and on *HIV virions* that have incorporated the host HLA-DR *protein* – much less an anti-HLA-DR antibody coupled to a liposome.

This is further supported by Saarloos –*as acknowledged by the Examiner* (Office Action at page 6, emphasis added):

> ...Saarloos et al. discloses that HLA-DR (Class II MHC) was associated with *in vivo* sources of HIV-1 virions from primary isolates, macrophages and blood plasma using an immunocapture method with an anti-HLA-DR antibody, the results showed that the anti-HLA-DR antibody captured about 50% of HIV Ada-M and HIVBa-L monocytotropic virus, and four of eight samples of plasma virus did not detectably bind to the anti-HLA-DR antibody (See Saarloos at page 1641, 2nd col., 2, 2nd ¶). At most, Saarloos' disclosure presents an "obvious-to-try" situation. *Given the unpredictability of the binding of an anti-HLA-DR antibody with HIV-1 virions and the level of HLA-DR expression of monocytes according to Saarloos, one skilled in the art reading Saarloos' disclosure would not expect an anti-HLA-DR antibody would necessarily and inevitably bind to HLA-DR protein on both a cell and on HIV virus – much less an antibody coupled to a liposome.*

Saarloos discloses that HLA-DR (Class II MHC) was associated with *in vivo* sources of HIV-1 virions from primary isolates, macrophages and blood plasma using an immunocapture method with an anti-HLA-DR antibody. However, the results showed that the anti-HLA-DR antibody captured only abut 50% of HIV_{Ada-M} and HIV_{Ba-L} monocytotropic virus, and four of eight samples *of plasma virus did not detectably bind* to the anti-HLA-DR antibody (Saarloos at page 1641, 2nd col., 2nd ¶).

Saarloos further states that it was unexpected that HLA-DR was *not detected* on all plasma virus samples tested – and further indicated that *levels on monocytes can substantially decrease* during HIV infection, stating as follows (at page 1642, 1st col., 1st ¶):

> ...It was somewhat unexpected then, to find that HLA-DR was not detected on all of the plasma virus samples tested...Alternatively, it is possible that plasma virus from samples testing negative for HLA-DR was derived from cells that expressed lower levels of HLA-DR in vivo. *In fact, Clerici et al. have observed that HLA-DR levels on monocytes can substantially decrease during HIV infectin (7)... Thus, the variation in levels of HLA-DR expression on plasma virus may be due to the plasma virus budding from more than one cell type or, alternatively, from several subpopulations of one cell type.*

Saarloos' disclosure -- *which is part of the art* - supports Applicant's position that one skilled in the art would not expect that an anti-HLA-DR antibody would necessarily and inevitably bind to HLA-DR protein on both a cell and on HIV virus – *much less an antibody coupled to a liposome.*

The disclosures of either Bergeron or Cantin do not overcome Saarloos' disclosure.

Given the unpredictability of the binding of an anti-HLA-DR antibody with HIV-1 virions and the level of HLA-DR expression in monocytes according to the prior art of record, there would be no reasonable expectation of success that a *liposome-bound* anti-HLA-DR antibody will be reactive against *both* HIV-1 virus *and cells.*

At most, Bergeron's disclosure presents an "obvious-to-try" situation.

With respect to obvious to try, two types of errors are generally recognized. *In re Fine,* 5 USPQ2d 1596, 1599 (Fed. Cir. 1988); *In re O'Farrell,* 7 U.S.P.Q. 2d 1673 (Fed. Cir. 1988). The error committed by the Examiner is the case in which what "is obvious to try" is to explore a new technology or general approach that seems to be a promising field of experimentation where the prior art (Bergeron) gave only general guidance and does not contain a sufficient teaching of how to obtain the desired result, or that the claimed result would be obtained if certain directions were pursued. *In re Eli Lilly & Co.*; 14 USPQ2d 1741, 1743 (Fed. Cir. 1990).

Although Bergeron's disclosure *may* suggest further investigation, one reading Bergeron would investigate an antibody that targets specific *cells* – and would not be motivated to utilize antibody 2.06 of Cantin, which was used to target special *HIV-1 particles —not cells.*

The cited references do not provide adequate guidance to provide a formulation as claimed composed of a liposome-bound anti-HLA-DR antibody reactive with both an infectious agent and cells.

The added disclosures of Desormeaux and/or Harlow do not make up for the deficiencies of Bergeron with Cantin.

Nothing in the cited references, either alone or in combination, disclosure or suggest the presently claimed formulations, and withdrawal of the rejections of the claims is respectfully requested.

Extension of Term.

The proceedings herein are for a patent application and the provisions of 37 CFR § 1.136 apply. Applicant believes that a one-month extension of term is required. Please charge the required fee (large entity) to Account No. 23-2053. If an additional extension is required, please consider this a petition therefor, and charge the required fee to Account No. 23-2053.

It is submitted that the present claims are in condition for allowance, and notification to that effect is respectfully requested.

Respectfully submitted,

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